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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
DARIO CREMASCHI, ET AL.	: EXAMINER: NICKOL, G.B.
SERIAL NO: 09/988,150	:
FILED: NOVEMBER 19, 2001	: GROUP ART UNIT: 1642
FOR: USE OF MICROPARTICLES HAVING A PROTEIN AND AN ANTIBODY ADSORBED THEREON FOR PREPARING A PHARMACEUTICAL COMPOSITION FOR INTRANASAL ADMINISTRATION	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This brief is submitted in response to the rejection dated March 9, 2005.

REAL PARTY OF INTEREST

The real party of interest herein is Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. S.p.A, of Roma, Italy.

RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 11-13, 15-22, and 24-28 are pending. Claims 22 and 24-28 have been indicated as being allowable in the Office Action dated March 9, 2005. Claims 11-13 and 15-19 are rejected. Claims 20 and 21 are objected.

STATUS OF AMENDMENTS

There are no outstanding amendments that have not been entered in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is to a method for intranasally administering a composition comprising a microparticle having a protein and an antibody specific for the protein adsorbed thereon, by contacting a microparticle having a protein and an antibody thereon with the nasal mucosa of a patient in need thereof.

This method provides an efficient means of presenting the microparticles to a patient and yield significantly better results than methods previously employed. Significantly, as described on page 4, line 4 of the present specification, the claimed method provides 400,000 times higher levels than administration in the intestine.

GROUND OF REJETION TO BE REVIEWED ON APPEAL

Issue # 1

The rejection to be reviewed on appeal is of Claims 11-13 and 15-19 under 35 U.S.C. § 103 in view of Smith et al (WO94/28879), Bomberger (U.S. 5,879,712) and Almeida et al (J. Drug Targeting, 1996, vol. 3, pages 455-467).

Issue # 2

The objection to be reviewed on appeal is of Claims 12 and 21 under 37 C.F.R. 1.75(c) as allegedly being improper dependent claims.

ARGUMENT

Issue #1

The claimed invention is not obvious for two reasons. First, the combination of Smith Bomberger and Almeida do not provide the requisite motivation to perform the claimed method, i.e., intranasal administration of the composition comprising a microparticle having a protein and antibody adsorbed thereon as required in Claim 1. Second, the combination of cited prior art provide no suggestion or reasonable expectation for the vast improvement for the delivery of the composition defined in Claim 11 when delivered through the nasal mucosa relative to the intestinal mucosa, which data are of record in the present application. These points are further elaborated upon in the remarks below with reference to the cited prior art and the present specification.

Smith is described in the present specification on page 2, last paragraph. Smith describes a composition of a protein and an antibody absorbed on a microparticle (page 736, last paragraph). Smith describes administering this composition to the intestine (see "Summary" on page 735, "Experimental" on page 736, "Microsphere uptake by intestinal M cells" on page 737, and "Discussion" on pages 741-742). Smith does not describe intranasal administration.

For intranasal administration, the Office has cited Bomberger and Almeida and has alleged that one would employ the Smith composition intranasally based on the suggested advantages of nasal delivery in Bomberger and Almeida (page 457, col. 1 of Almeida). This assertion is untenable for the following reasons.

The combined teachings of the cited references do not suggest the present method of intranasal administration and as such fail to support a *prima facie* case of obviousness. In particular, while Almeida, on page 457, col. 1, describes several advantages of administering

drugs nasally, a further reading of Almeida reveals the following on page 471, second column, second paragraph (emphasis added):

> The mode of entry of nasally administered particles into the circulation is not fully understood and few investigators have postulated putative mechanisms (Kuper et al., 1992). The nasal adsorption of fluorescent polystyrene particles has been observed, which suggests that the mechanism of solid particle uptake by the nasal mucosa is **similar** to that found in the gut (Alpar et al., 1994).

Thus, while Almeida generally describes drugs on page 457, when Almeida specifically discusses the administration of particles, the claimed invention employs microparticles, Almedia suggests that absorption to through the intestinal and nasal mucosa are similar.

Furthermore, Bomberger also fails to provide any disclosure relevant to the obviousness of the claimed invention. In particular, Bomberger describes a microparticle having controlled degradation particles for the controlled delivery of drugs to the nasal passageway (col. 4, lines 8-51 and col. 6, lines 5-6 of Bomberger). This, however, is not all that Bomberger describes. Throughout Bomberger's disclosure, the drug to be delivered is contained within the microparticle for this controlled delivery (see, e.g., col. 15, lines 29-31 of Bomberger). As noted above and shown in the appended claims, the composition has a protein and antibody adsorbed onto the microparticle NOT encapsulated within the microparticle as taught by Bomberger.

Therefore, the motivation to administer the Smith composition intranasally is based either on hindsight reconstruction of the present invention or under an obvious to try rationale, both of which are improper for establishing that the claimed invention would have been obvious. Furthermore, when combining the relevant disclosures of all three publications, the teachings, in fact, lead one away from the claimed invention because Bomberger

explicitly requires the drug to be contained within the microparticle as opposed to adsorbed thereon.

It is further noted, "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combinations".[1] The Patent Office can only satisfy its burden to establish a *prima facie* case of obviousness "by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references."[2] For the reasons set forth above, such teachings, suggestions or incentives are missing here.

In any case, even a *prima facie* case is rebutted by the data of record in the application which demonstrates greater than 400,000 times more microparticles absorbed through the nasal mucosa compared to the intestines. In particular, Appellants note the Office's guidelines for examination set forth in MPEP § 716.02(a): "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985).

The data are presented on pages 3, 4 and 11 of the present specification are summarized below:

(1) In the intestine: yield/cm^2 = 4.4 x 10^{-9} (=0.0000044°/oo) - page 3, line 28

(2) In the nasal mucosa: yield/cm^2 = 1.7 x 10^{-3} (=1.7°/oo) which is 400,000 times greater than the absorption in the intestine - page 11, lines 22-28.

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[1] In re Geiger, 815 F.2d 686, 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987).

[2] In re Fine, 837 F.2d 1071, 5 USPQ 2d 1596, 1598 (Fed. Cir. 1988).

As has been previously discussed, the comparisons provided in the specification performed *in vivo* at 37°C and the experiments performed for the nasal mucosa performed *in vitro* at 27°C are comparable and provide the following in support of this assertion.

As discussed on page 9, lines 25 to 27: "The incubation temperature was 27°C ± 1°C. As compared with 37°C, this temperature lowers metabolism and transport twice as much, but renders the isolated tissue more stable." Since microparticle transport at 27°C is 400,000 times greater than transport in the intestine at 37°C (page 11, lines 22-28), it would be expected that if the experiments in the nasal mucosa were performed at 37°C the resulting increase through the nasal mucosa would have been approximately 800,000 times greater than the intestine. Clearly, this result is even more dramatic and is greater than an expected result. Additionally, it is noted that since the nasal mucosa (nostril) is exposed and not as well insulated by the body (compared to an internal organ such as the intestine), the temperature of the nasal mucosa is more susceptible to changes in the ambient temperature. For example, if the ambient temperature is approximately 22°C, the temperature of the nostril would be approximately 32°C and as the ambient temperature declines, the nostril temperature will also decline. Thus, the experimental conditions of 27°C more closely mimics the real temperature of the nasal mucosa in a living individual.

Turning to the issue comparing *in vitro* testing and *in vivo* testing, the comparison of *in vivo* intestinal data and *in vitro* nasal mucosa data is appropriate. Intestinal tissue isolated for *in vitro* testing consists of mono-layered epithelium, a layer of connective tissue underneath (which contains the ducts and thick lymphoid tissue of the Peyer's patches), two layers of musculature, another layer of connective tissue and a serous membrane. *In vivo* the proteins are adsorbed by intestinal epithelium, then pass into connective tissue where they then reach the ducts and where the microparticle numbers are measured (see page 3, lines 20-

23). Contrast this adsorption pathway to the adsorption *in vitro*, where the proteins have to pass through the whole wall of the isolated intestine before being measured and thus much of the proteins to be measured are lost. Accordingly, the absorption of proteins in the intestine is significantly more efficient *in vivo* than *in vitro*. The nasal mucosa membranes isolated for *in vitro* testing consists of a psuedoepithelium layer and a thin layer of connective tissue. Thus, the adsorbed protein passes through the nasal mucosa in much the same way both *in vitro* and *in vivo*, *in vivo* the protein reaches the ducts whereas *in vitro* the protein passes through the thin layer connective tissue.

Accordingly, comparing transport in the nasal mucosa *in vitro* at 27°C with the transport in the intestine *in vivo* at 37°C is physiologically more correct than comparing transport of the two tissues both *in vitro* or *in vivo* at the same temperature.

It is submitted in view of the foregoing that the claimed invention, in Claims 11-13 and 15-19, are not obvious in view of the combined teachings of the cited references since the references fail to suggest this claimed method and the significant absorption of the microparticle composition in the nasal mucosa when compared to the absorption of the same microparticle composition in the intestine.

Accordingly, in view of the above remarks and reasons explaining the patentable distinctness of the presently appealed claims over the applied prior art, Appellants request that the Examiner's rejections be REVERSED.

Issue #2

The second issue to be reviewed on appeal is the Examiner's allegation that Claims 12 and 21 improperly depend from Claims 11 and 20, respectively, "because the specification does not appear to differentiate between a "protein" and "polypeptides"." (Page 2 of the Official Action of March 9, 2005. This assertion is incorrect. The specification on page 1, lines 8-11 clearly differentiates those terms, in that, a polypeptide is a sub-category of protein:

> In the present description and the following claims, the term "protein" comprises any compound of condensation of two or more amino acids. The term therefore comprises, but is not limited to, biologically active peptides, polypeptides and proteins.

In fact, these terms, as used in the specification, are consistent with common usage in the art. A polypeptide is "A linear molecule composed of two or more amino acids linked by covalent (peptide) bonds whereas a "protein" is a macromolecule composed of one to several polypeptides." (see the attached evidence listed in Appendix II, which is a print out of entries from "A Glossary of biotechnology and genetic engineering).

Accordingly, and in view of the above remarks and attached evidence, Appellants request that the Examiner's objection be withdrawn.

Respectfully submitted,

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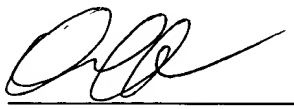

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APPENDIX 1 (CLAIMS)

Claims 1-10 (Cancelled).

11. (Rejected) A method for intranasally administering a composition comprising a microparticle having a protein and an antibody adsorbed thereon, wherein said administering comprises contacting a microparticle having a protein and an antibody thereon with the nasal mucosa of a patient in need thereof, wherein said antibody is an immunoglobulin specific for the protein.

12. (Rejected) The method of Claim 11, wherein said protein is selected from the group consisting of BSA, insulin, enkephalin, hormones, growth factors, cytokines, coagulation factors, polypeptides, and antimicrobial agents.

13. (Rejected) The method of Claim 11, wherein said antibody is an immunoglobulin selected from the group consisting of IgM, IgA, and IgG.

Claim 14 (Cancelled).

15. (Rejected) The method of Claim 11, wherein said microparticle is biodegradable.

16. (Rejected) The method of Claim 11, wherein said microparticle comprises polystyrene.

17. (Rejected) The method of Claim 11, wherein the ratio of protein to antibody is 1 to 15,000 moles of protein per mole of antibody.

18. (Rejected) The method of Claim 11, wherein the ratio of protein to antibody is 1 to 5,000 moles of protein per mole of antibody.

19. (Rejected) The method of Claim 11, wherein the ratio of protein to antibody is 1 to 100 moles of protein per mole of antibody.

20. (Rejected) A method for intranasally administering a composition comprising a microparticle and an antibody adsorbed thereon, wherein said administering comprises having a protein and an antibody thereon with the nasal mucosa of a patient in need thereof, and wherein the transepithelial transport obtained with 3.2×10^{11} microparticles/ml is $1.7^{o}/_{oo}$, wherein said antibody is an immunoglobulin specific for the protein.

21. (Rejected) The method of Claim 20, wherein said protein is selected from the group consisting of BSA, insulin, enkephalin, hormones, growth factors, cytokines, coagulation factors, polypeptides, antimicrobial agents.

22. (Allowed) The method of Claim 20, wherein said antibody is an immunoglobulin selected from the group consisting of IgM, IgA, and IgG.

Claim 23 (Cancelled).

24. (Allowed) The method of Claim 20, wherein said microparticle is biodegradable.

25. (Allowed) The method of Claim 20, wherein said microparticle comprises polystyrene.

26. (Allowed) The method of Claim 20, wherein the ratio of protein to antibody is 1 to 15,000 moles of protein per mole of antibody.

27. (Allowed) The method of Claim 20, wherein the ratio of protein to antibody is 1 to 5,000 moles of protein per mole of antibody.

28. (Allowed) The method of Claim 20, wherein the ratio of protein to antibody is 1 to 100 moles of protein per mole of antibody.

APPENDIX II (EVIDENCE)

Polypeptide and Protein entries in "Glossary of biotechnology and genetic engineering" FAO Research and Technology Paper No. 7

(http//www.fao.org/documents/show_cdr.asp?url file=//DOCREP/003/X3910E/X3910E19.htm)

ENCL. 1

FAO RESEARCH AND TECHNOLOGY PAPER No. 7

Glossary of biotechnology and genetic engineering

Polypeptide A linear molecule composed of two or more amino acids linked by covalent (peptide) bonds. They are called dipeptides, tripeptides and so forth, according to the number of amino acids present.

Protein (Gr. *proteios*, of the first rank) ***A macromolecule composed of one to several polypeptides***. Each polypeptide consists of a chain of amino acids linked together by covalent (peptide) bonds. They are naturally-occurring complex organic substances (egg albumen, meat) composed essentially of carbon, hydrogen, oxygen and nitrogen, plus sulphur or phosphorus, which are so associated as to form sub-microscopic chains, spirals or plates and to which are attached other atoms and groups of atoms in a variety of ways. The word was coined by Jöns J. Berzelius (1838) to emphasize the importance of this group of molecules. *See* polypeptide.

http://www.ornl.gov/sci/techresources/Human_Genome/glossary/glossary_p.shtml

Genome Glossary

Polypeptide

A protein or part of a protein made of a chain of amino acids joined by a peptide bond.

Protein

A large molecule composed of one or more chains of amino acids in a specific order; the order is determined by the base sequence of nucleotides in the gene that codes for the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs; and each protein has unique functions. Examples are hormones, enzymes, and antibodies.